

REMARKS/ARGUMENTS

Applicants submit the aforementioned amendments and following remarks in response to the Final Office Action mailed January 22, 2008. A petition for extension of time for responding to the aforementioned Office Action is requested.

A Request For Continued Examination (RCE) is being filed concurrently herewith.

Claim 7 is pending and amended. No new matter is added. Reconsideration is respectfully requested in view of the above amendments and the following remarks.

Rejection under 35 U.S.C. § 103(a)

The Examiner maintains the rejection of claim 7 under 35 U.S.C. § 103(a) over Condra et al., in view of admitted prior art, de Bethune et al., Seki et al., and Bakhanashvili et al. Specifically, the Examiner cites that (1) Condra et al. discloses the 88T mutation correlates with reduced effectiveness of IDV protease inhibitor, (2) the Background section of the present application discloses HIV therapy includes the combination of protease inhibitor (PI) and reverse transcriptase inhibitor (RTI), (3) de Bethune et al. discloses the 101Q mutation in resistance to a non-nucleoside reverse transcriptase inhibitor (NNRTI), (4) Larder et al. discloses the 69S-[S-S] mutation in resistance to a nucleoside reverse transcriptase inhibitor (NRTI), and (5) Bakhanashvili et al. discloses the Met 184 to Leu mutation in reverse transcriptase. The Examiner also cites Seki et al. but does not clearly articulate the reason why the claimed method would have been obvious in view of Seki et al.

The Examiner recognizes Condra et al. does not teach the resistance conferred by mutation in reverse transcriptase. However, the Examiner states a skilled artisan is motivated to combine mutations described in the above documents to evaluate the effectiveness of therapy by determining the presence of mutation 88T in the protease, and mutations 101Q, 69S-[S-S], 184L in the reverse transcriptase.

Also with regard to Condra et al., the Examiner states that the step c) is drawn to “at least one” mutation and therefore reads on situation wherein the recited mutation is one of several others in Condra et al. Applicants respectively submit that claim 7 has been amended

previously to recite “a third nucleic acid encoding an HIV-1 protease comprising: 1) mutation 88T; or 2) a combination of mutations 33F and 90M, in which the presence of said third nucleic acid correlates with resistance to a Protease Inhibitor (PI)”. See Response submitted November 8, 2007, page 2. Applicants respectively request for a clarification.

Condra et al. discloses at least thirty (30) HIV mutations including 88T that render resistance of HIV to indinavir (IDV), a HIV PI. See Table 1. Condra et al. also analyzes the correlation between the genotype of amino acid substitution and the phenotype of the PI resistance, and shows a single amino acid substitution or mutation does **not** render any measurable resistance. This is explicitly stated on page 8271, last paragraph: “Over all, the data demonstrated that no single pattern of amino acid substitutions in the viral protease was required for the development of resistance to IDV”. This finding is repeated consistently throughout Condra et al. For example, page 8275, last paragraph: “In conclusion, the development of IDV resistance has been shown to occur through multiple, overlapping genetic pathways, and this resistance results from the combined effects of several mutations that do not confer a measurable degree of resistance when occurring alone”; and page 8270, Abstract: “**No single substitution or pair of substitutions tested gave rise to measurable viral resistance to IDV**”. Emphasis added.

Clearly, Condra et al. suggests that the degree of resistance to PI in the presence of the 88T mutation in HIV-1 protease is not measurable. It follows that 88T mutation in the HIV protease does not correlate with the resistance to a PI, according to Condra et al. Thus Condra et al. **teaches away** from the present invention, which teaches that each mutation recited in claim 7, **individually**, is measured to correlate with the drug resistance.

De Bethune et al. discloses at least thirteen (13) HIV mutations that are resistant to NNRTI. De Bethune et al. also discloses the patient 24 with a K101Q genotype. De Bethune et al. does not disclose or suggest that HIV-1 protease mutation be useful to evaluate therapy effectiveness as recited in claim 7.

Larder et al. discloses at least eight (8) RT mutations including 69S-[S-S] that are resistant to a NRTI such as AZT. Larder et al. does not disclose or suggest that HIV-1 protease mutation be useful to evaluate therapy effectiveness as recited in claim 7.

Bakhanashvili et al. studies mutations in a reverse transcriptase, including M184L, in the accuracy of DNA synthesis. Bakhanashvili et al. does not disclose any mutation recited in claim 7.

Though the Examiner does not discuss Seki et al, Applicants describe Seki et al. herein for the purpose to expedite the prosecution. Seki et al. examines mutation resistant to a NNRTI. Seki et al. discloses the presence of three mutations, T181C, K103R and V108I, in a resistant virus. Seki et al. does not disclose or suggest that HIV-1 protease mutation be useful to evaluate therapy effectiveness as recited in claim 7.

As discussed above, de Bethune et al., Larder et al., Bakhanashvili et al., and Seki et al. are all silent in the use of HIV-1 protease mutation, including 88T, to predict its resistance to PI for evaluating therapy effectiveness as set forth in the claimed method. Therefore, the deficiency in Condra et al. is not cured by any of the above documents.

Further the present invention is directed to a ***method of evaluating the effectiveness of a drug therapy by identifying a specific set of mutations in the protease and reverse transcriptase of the HIV virus***, as opposed to a combination therapy of PI and NRTI or NNRTI.

As discussed above, none of the cited documents expressly or implicitly makes any connection between the protease mutations and the reverse transcriptase mutations. That being said, even assuming that there is a general motivation for a person skilled in the art to look into both types of mutations when evaluating the effectiveness of HIV therapy, it remains a question that which mutations a person of skilled in the art ought to look into. While the number of possible combinations of the mutations within the cited documents can be numerous, the present invention is directed to a selected set of mutations in the reverse transcriptase and the protease. This particular set of mutations did not logically come out of the combined documents or any common knowledge, nor is there any reason for anyone to select these mutations. To further illustrate, the probabilities of choosing the mutations of 88T from Condra et al., 101Q from de Bethune et al., and 69S-[S-S] Larder et al. is less than 0.03% ($1/30 \times 1/13 \times 1/8 = 0.03\%$). This calculation does not even take the other mutations into account, which, if done, would further reduce the chance of this selection. In addition, Condra et al. teaches away from the present invention. Thus, a person skilled in the art, who is confronted with the same problem, would not

be able to combine the cited documents and the mutations in the same way as Applicants, absent the knowledge of the present application.

The Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. § 103 should be made explicit and rejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. *KSR Int'l Co. v. Teleflex, Inc.*, 82 USPQ2d at 1395. The Examiner has not articulated any reason why the cited documents should be combined other than a conclusory statement. In view of the *KSR* case, Applicants respectfully submit that it is improper to form the 103 rejection solely based on the presence of mutations without a clear explanation how the presence of the mutations would lead the skilled artisan to combine them.

Accordingly, the rejection under 35 U.S.C. § 103(a) has been overcome and should be withdrawn.

In view of the foregoing amendments and remarks, allowance of claim 7 is respectfully requested.

Respectfully submitted,

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